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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,849	06/27/2002	William Hugold Velander	TRANS 1	2472

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of June 25, 2008 on October 20, 2008. Claims 1-39, 41, 43, 45, 47-55, 59, 60 are cancelled. Claim 40 is amended.

Claims 40, 42, 44, 46, 56-58, 61, drawn to a composition comprising milk derived from a transgenic mammal and a recombinant human prothrombin, wherein the Gla domain of prothrombin is gamma-carboxylated, are under consideration.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 61 remain rejected in modified form under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, Seegers et al., 1950, Blood, 5: 421-433, previously cited, van Cott and Velander, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS.

It is noted that Applicant has amended claim 40 to include a new limitation. As such, the Examiner will address the amendment to claim 40 as follows. Response to Applicant's rebuttals follows the Examiner's discussion of claim 40.

As discussed in the Office Action of June 25, 2008, pages 4-6, the combination of Meade et al., Jorgensen et al., Seegers et al., and van Cott and Velander provides guidance to arrive at a composition comprising milk derived from a transgenic mammal and recombinant protein comprising human prothrombin, wherein its Gla domain is completely gamma-carboxylated. However, the teachings do not provide guidance for the recombinant protein having a concentration of at least 0.5 mg/ml. At the time of filing, Velander et al. teach that recombinant protein expressed in the milk of transgenic pigs can be expressed as high as 1000ug/ml (Velander et al., page 12005, 1st col., parag. under "Protein Analysis", see also Figure 1). As such, all of the component parts are taught by Meade et al., Jorgensen et al., Seegers et al., van Cott and Velander, and Velander et al. The only difference is the combination of the “old references” into a mammalian system which produces recombinant human prothrombin, wherein its Gla domain is gamma-carboxylated, in milk. An artisan would have combined these teachings in order to arrive at a way of making more recombinant prothrombin.

Applicant's arguments filed October 20, 2008 have been fully considered but they are not persuasive.

Applicant indicates that the Examiner asserts a new reference (Meade et al.) in combination with previously asserted secondary references and object to this improper piecemeal examination strategy and asks why the Examiner is only now asserting the

reference if it was not considered relevant in the past (Applicant's response, page 4). In response, the examination was not piecemeal. Per MPEP 707.07(g), the claims were rejected on each claim on all valid grounds available, avoiding, however, undue multiplication of reference. Based on the search performed, Butler appeared as appropriate prior art and thus it was used in a 103 rejection, Office Action, April 23, 2007. Applicant persuasively argued that the Butler reference could not be used because it was not prior art, as it was not publicly available (Applicant's response, November 5, 2007). As such, the rejection over Butler was withdrawn. The question was then raised as to whether the claims were free of the art. Because there is art (Meade et al.) applicable to the rejection of the claims, the rejection, at hand, was made.

Applicant indicates that the obviousness rejections depend upon an improper combination of Meade et al. and Jorgensen et al. Applicant indicates that the Examiner has not found all of the Applicant's claimed elements. Applicant indicates that the Examiner admits that Meade et al. do not teach all the claimed elements, wherein Meade et al. do not indicate that recombinant prothrombin is made in milk. Applicant submit that not only does Meade et al. not teach recombinant prothrombin in milk, Meade et al. also does not teach recombinant prothrombin comprising a fully carboxylated Gla domain in milk. To provide a prima facie case of obviousness, the Examiner must now provide a reference that supplies this missing element (Applicant's response, pages 5-6). In response, this is not persuasive. Given that Meade et al. and Jorgensen et al. provide guidance for making recombinant protein in milk and that the nucleic acid sequence encoding human prothrombin was known, an artisan would have

arrived at prothrombin that comprised a completely gamma-carboxylated Gal domain. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). It is noted that Meade et al. nor Jorgensen et al. are nor required to teach that the human prothrombin protein made in milk needed to be recognized as having a completely gamma-carboxylated Gla domain. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). It is also noted that the Examiner refers to the teaching of van Cott and Velander 1998 (Office Action, June 25, 2008, page 6), wherein the publication teaches that recombinant proteins expressed in milk are gamma-carboxylated. Because it was known that recombinant proteins expressed in milk are gamma-carboxylated, an artisan would have expected that recombinant prothrombin expressed in milk would also be gamma-carboxylated.

Applicant indicates that the Examiner has clearly not properly considered the scope and content of Jorgensen et al. because the reference has no context related to making and using transgenic animals using high protein expression platforms. This is the very issue that In re Kahn held against. Additionally, Jorgensen et al. provides context that teaches away from the Applicant's claimed embodiment (see Jorgensen et al., page 6733), wherein about 60% of the secreted prothrombin is carboxylated. In response, this is not persuasive. With regard to Applicant indicating that Jorgensen et al. do not teach context of making and using transgenic animals to overexpress protein, Applicant is correct that Jorgensen et al. do not teach using transgenic animals to make recombinant protein. However, the rejection at hand is not a 102, but is a 103 and the Examiner relies on Meade et al. for teaching expression of recombinant protein in milk. With regard to Applicant indicating that Jorgensen et al. teach away from the claimed invention, Jorgensen et al.'s teaching indicates that large amounts of protein is made in cultured CHO cells that the enzymes that carboxylate prothrombin cannot keep up with all the recombinant protein that is to be carboxylated. This does not teach away from making carboxylated protein because the cells do, in fact, carboxylate prothrombin protein.

With regard to Applicant indicating that the claims have been amended to include the phrase, "at least 0.5 mg/ml" of prothrombin (Applicant's response, page 7), the Examiner has addressed the rejection as it applies to this limitation, as discussed above.

Applicant indicates that the Examiner has not shown that Seegers et al. remedies the deficiencies of Meade et al. and Jorgensen et al. by teaching a highly expressed fully carboxylated recombinant prothrombin (Applicant's response, page 8). In response, this is not persuasive. As discussed above, Velander et al. provide guidance that transgenic mammals produce recombinant proteins at concentrations of at least 0.5 mg/ml. As such, the claims are obvious. With regard to Seegers et al., it is noted that Seegers et al. was cited to indicate that there was a reason why artisans would have wanted to make recombinant protein in milk. That reason was because artisans were interested in making large amounts of prothrombin to study its role in blood clotting (Office Action, June 25, 2008, page 5).

With regard to van Cott et al., Applicant indicates that the Examiner has ignored the fact that van Cott et al. were not discussing the gamma-carboxylation of prothrombin, and that the claims are directed to prothrombin. In addition to this, the prothrombin expression level, as recited in claim 40 is 5 times superior to that referred to in van Cott et al. (Applicant's response, page 8). In response, this is not persuasive. van Cott et al. is not a 102 rejection. van Cott et al. was used to illustrate that recombinant proteins expressed in milk are gamma-carboxylated. As such, expression of prothrombin in milk of recombinant mammals would have been gamma-carboxylated. With regard to the concentration of recombinant protein expressed in milk, the Examiner has addressed this issue, see above, Velander et al., 1992.

Thus, the claims remain rejected.

Claims 40, 42, 44, 46, 56, and 58 remain rejected in modified form under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS.

Applicant's arguments filed October 20, 2008 have been fully considered but they are not persuasive.

With regard to Le Bonniec et al., Applicant indicates that Le Bonniec et al. do not remedy the lack of a prima facie case of obviousness in view of the other asserted references. Specifically, Le Bonniec et al. does not provide any evidence teaching recombinant prothrombin in the milk of a transgenic mammal having a concentration of at least 0.5 mg/ml (Applicant's response, pages 8-9). In response, this is not persuasive. As discussed above, Velander et al. provide guidance that recombinant protein can be expressed at concentrations of at least 0.5 mg/ml.

Thus, the claims remain rejected.

Claims 40 and 57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, in view of Seegers et al., 1950, Blood 5: 421-433, previously cited, Le Bonniec et

al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS.

Applicant's arguments filed October 20, 2008 have been fully considered but they are not persuasive.

Applicant provides no specific arguments to the combination of rejection, above. With regard to Applicant's arguments as they apply to Meade et al., Jorgensen et al., Seegers et al., and Le Bonniec et al., the Examiner has responded to Applicant's rebuttals.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Primary Examiner
Art Unit 1632